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ORIGINAL ARTICLE

Renal function after combined liver-kidney transplantation: A longitudinal study of pediatric and adult patients

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Abstract

It has been proposed that the liver protects the kidney in CLKT. However, few studies have examined long-term renal function after CLKT and contrasted renal function of CLKT patients to KT patients beyond one year after transplantation. We studied long-term renal function of CLKT patients and compared renal function of CLKT patients to KT patients between one and five years after transplantation. Patients who underwent CLKT between 1993 and 2011 were included ($n = 34$; 11 children and 23 adults). Ninety-six (27 children and 69 adults) KT patients were selected as controls. GFR was estimated (eGFR) and measured (mGFR) with ^{51}Cr -EDTA clearance. Mean mGFR was 63 at one and 70 at ten years after pediatric CLKT. Mean eGFR was 75 at one and 50 at ten years after adult CLKT. Difference in mean mGFR between pediatric CLKT and KT patients was 8 (95% CI -7 to 23) and 11 (95% CI -4 to 26) at one and five years after transplantation, respectively. Difference in mean eGFR between adult CLKT and KT patients was 8 (95% CI -5 to 20) and 1 (95% CI -10 to 12) at one and five years after transplantation, respectively. Longitudinal changes in GFRs were somewhat similar in CLKT and KT patients in both age-groups but pediatric CLKT patients had on average higher GFRs than pediatric KT patients. In long-term follow-up, renal function remains stable in pediatric CLKT patients but declines in adult CLKT patients.

KEYWORDS

adult, combined liver-kidney transplantation, glomerular filtration rate, kidney transplantation, pediatric

1 | INTRODUCTION

CLKT is a preferred option for patients with chronic organ failure altering both the liver and the kidney according to a hepatocentric

approach.¹ More than 8000 CLKTs have been performed, more than 300 of them to pediatric patients in the United States to date.² In Scandinavia, 0.5% (10/1915) of transplanted patients received combined liver and kidney transplants in 2016.³ Large registry studies have reported five-year patient survival of 76% and 82% after adult and pediatric CLKT, respectively.^{4,5}

Five-year cumulative incidence of CKD, depending on definition and population, varies from 3% to 18% after LT.⁶⁻⁸ The prevalence of CKD was 25% up to six months after CLKT in small study.⁹ We have previously shown that GFR remains relatively stable from one up to five years after adult and pediatric LT and also after pediatric KT.¹⁰⁻¹² Others have

Abbreviations: ^{51}Cr -EDTA, 51-chromium-labeled ethylenediaminetetraacetic acid; AZA, azathioprine; CI, confidence interval; CIT, cold ischemia time; CKD, chronic kidney disease; CLKT, combined liver-kidney transplantation; CNF, congenital nephrotic syndrome of Finnish type; CsA, cyclosporine A; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; IQR, interquartile range; KT, kidney transplantation; LOA, limits of agreement; LT, liver transplantation; mGFR, measured glomerular filtration rate; MMF, mycophenolic acid; MP, methylprednisolone; PKD, polycystic kidney disease; SD, standard deviation; TAC, tacrolimus.

reported that GFR remains steady or slightly worsens up to five years after adult and pediatric CLKT.¹³⁻¹⁶ Only few studies have contrasted renal function of CLKT patients to renal function of KT patients, especially with a follow-up period beyond one year after transplantation.^{15,16}

Our aim was to study long-term renal function in pediatric and adult CLKT patients in a single center. We also compared renal function of CLKT patients to renal function of KT patients in both age-groups separately between one and five years after transplantation.

2 | MATERIALS AND METHODS

2.1 | Patients

All adult and pediatric (age ≤ 16 years) patients who underwent deceased donor CLKT between 1993 and 2011 at Helsinki University Hospital (HUH) were included in our longitudinal study ($n = 34$; 23 adults and 11 children). One pediatric patient deceased less than one month after CLKT; 10 pediatric patients were thus included in the final analyses. The clinical follow-up of these patients is organized by the Departments of Transplantation and Liver Surgery (adult unit) and Pediatric Nephrology and Transplantation (pediatric unit). Both of these departments are a part of HUH where all transplantations in Finland are performed, more than 8000 KT and more than 1000 LT to date. The first CLKT for an adult and pediatric patient was performed in 1993 and 1999, respectively.

Three KT patients were selected as controls for every CLKT patient. Control patients were matched with regard to gender, age at transplantation (\pm two years) and transplantation year (\pm two years). Instances in which more than three control patients were matchable (ie, same gender, age at transplantation within \pm two years and transplantation year within \pm two years), selection of three controls was primarily based on age so that age instead of transplantation year was kept as close as possible between the CLKT and KT patients. In addition, pediatric patients were matched (if feasible) within pubertal stage (ie, a prepubertal CLKT patient was not matched with a pubertal KT patient). Control patients with a re-transplant, transplant from a living donor, follow-up less than one year after transplantation, and with congenital nephrosis of the Finnish type with recurrent nephrosis were excluded. All control patients were manually selected from the list of consecutive KT in Finland.

Patients' medical records and national transplantation registry were used to retrieve clinical information. This study is part of research projects which have been approved by the ethics committees of the Hospital District of Helsinki and Uusimaa (application number 345/13/03/03/2008 and 268/13/03/02/2010).

2.2 | Immunosuppression

Triple immunosuppression with CsA, AZA, and MP was used as initial immunosuppression. CsA was switched to TAC and AZA to MMF on an individual basis if clinically indicated. In pediatric patients, basiliximab was used as induction since 1999.

In adults, MMF was used since 2006 and TAC was given to immunologically unstable patients and if patient was in a trial. In addition, MP withdrawal was target within 12 months except in autoimmune liver diseases in adult patients.

For pediatric patients, CsA and TAC target trough levels were 60 to 100 $\mu\text{g/L}$ and 4 to 6 $\mu\text{g/L}$, respectively, at one year after transplantation and thereafter. For adult patients, CsA and TAC target trough levels were 70 to 150 $\mu\text{g/L}$ and 5 to 10 $\mu\text{g/L}$, respectively, at one year after transplantation and thereafter.

Immunosuppression at one year after transplantation, and CsA and TAC trough levels at one, three and five years after transplantation are shown in Tables S1 and S2.

2.3 | Acute kidney rejections

Acute kidney rejections were recorded up to three months after transplantation since most of these rejections occur within this time-frame. Data on these rejections are also more thorough in medical records or in our national transplantation registry. Diagnosis of rejection was based on fine-needle aspiration or core-needle biopsy.

2.4 | Renal function

GFR was measured (mGFR) with plasma⁵¹Cr-EDTA clearance as part of routine clinical follow-up for both pediatric CLKT and KT patients, and cross-sectionally as part of the study in a subsample of adult CLKT patients. Measured GFRs taken before the end of January 2006 were corrected for one-pool approximation with an averaged Bröchner-Mortensen Equation.¹⁷ GFR was estimated (eGFR) with the bedside Schwartz equation [$0.413 \times (\text{height (cm)}/\text{creatinine (mg/dL)})$]¹⁸ in pediatric patients and with the CKD-EPI Equation¹⁹ in adult patients.

Throughout, GFRs are shown as rounded to the nearest whole number unless otherwise specified and with the unit of $\text{mL}/\text{min}/1.73 \text{ m}^2$.

2.5 | Statistics

Statistical analyses were performed with Stata 12.1 (StataCorp LP, College Station, TX, USA) and R 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are presented as means and SD and as medians and IQR if indicated. IQRs were calculated with the method recommended by Hyndman et al²⁰ Survival curves were constructed with the Kaplan-Meier method.

Comparison of mean GFRs between CLKT and KT groups was conducted separately for time-points at one, three, and five years after transplantation with Welch's *t* test (primary GFR analysis). In addition, comparison of mean change of GFRs (ie, obtaining GFR change for every patient and taking mean change across all patients) from one to three (GFR at three minus one) and three to five (GFR at five minus three) years after transplantation between CLKT and KT groups was conducted with Welch's *t* test (secondary GFR analysis). In sensitivity analysis, due to potential skewness of GFRs, medians were compared according to the Bonett-Price method²¹ with a user-written Stata module.²²

In additional GFR analysis for adult patients, linear mixed models were specified with eGFR as a response variable and group as a main predictor variable. Matched factors (ie, age at transplantation, gender, and transplantation year) were also adjusted. Random intercept models were specified in such a way that patients ($n = 92$ with 263 eGFRs) were nested within clusters ($n = 23$; ie, one CLKT patient and three KT control patients within one cluster). Mixed model analyses were carried out with R packages lme4 and lmerTest.^{23,24} Additional details are provided in Table S3. Residuals were inspected with quantile-quantile plots, and no severe deviation from normality was observed.

A pairwise comparison of mean GFRs at one to ten years after CLKT was conducted with paired t test. In sensitivity analysis to check robustness of CI for difference in pairwise means, bootstrap with 5000 resamples was used to obtain bias-corrected and accelerated CIs.

Comparison of two GFR methods (ie, eGFR and mGFR) with LOA was made with a user-written Stata module.²⁵ Correlation coefficients between eGFRs and CsA/TAC trough levels were calculated with a user-written Stata module.²⁶

3 | RESULTS

3.1 | Patients

The characteristics of the 34 CLKT patients are shown in Table 1. Of the 11 pediatric CLKT recipients, six (54.5%) were transplanted with reduced-sized liver grafts. One pediatric CLKT patient deceased less than one month after transplantation, which is why KT control patients were only selected for 10 CLKT pediatric patients. A total of 27 pediatric KT control patients were selected due to overlapping patients (two or three control patients for every pediatric CLKT patient). The characteristics of the 96 control KT patients are shown in Table 2. Mean donor age of the 10 pediatric CLKT patients was lower compared to pediatric KT patients (16.2 years versus 37.8 years). Difference in donor age was more evident with medians (11.3 versus 39.0). Age at the time of transplantation was similar in both adult (44.4 and 44.8 years) and pediatric (5.3 and 4.9 years) patients between CLKT and KT groups.

Of the 10 pediatric CLKT patients, three (30.0%) had biopsy-confirmed acute cellular kidney rejections compared to nine (33.3%) pediatric KT patients up to three months after transplantation. On the contrary, none of the adult CLKT patients experienced acute cellular kidney rejections compared to 10 out of 69 (14.5%) adult KT patients up to three months after transplantation.

3.2 | Survival of CLKT patients

Five-year patient survival was 91% (95% CI 51% to 99%) for pediatric and 96% (95% CI 73% to 99%) for adult CLKT patients (Figure 1). Nine patients (26.5%; two pediatric and seven adult) deceased during the follow-up.

TABLE 1 Characteristics of 34 CLKT patients

	Adult patients (N = 23)	Pediatric patients (N = 11)
Gender, n (%)		
Male	11 (47.8)	4 (36.4)
Female	12 (52.2)	7 (63.3)
Mean (SD) age at CLKT, years	44.4 (16.7) ^a	4.9 (4.3) ^b
Mean (SD) CIT, hours		
Liver	6.6 (2.5) ^c	5.4 (1.7) ^d
Kidney	11.3 (2.9) ^e	8.1 (1.8) ^f
Mean (SD) donor age, years	37.2 (15.2) ^g	16.6 (14.4) ^h
CLK as first transplant, n (%)		
Yes	16 (69.6)	8 (72.7)
No	7 (30.4)	3 (27.3)
Primary indication for CLKT, n (%)		
PKD	6 (26.1)	7 (63.6)
Metabolic disorder	-	3 (27.3)
Alcoholic cirrhosis	3 (13.0)	-
Chronic liver rejection	3 (13.0)	-
Cryptogenic cirrhosis	2 (8.7)	-
Other	9 (39.1)	1 (9.1)
CLKT era, n (%)		
1992-1996	1 (4.3)	-
1997-2001	5 (21.7)	2 (18.2)
2002-2006	12 (52.2)	4 (36.4)
2007-2011	5 (21.7)	5 (45.5)

One pediatric CLKT patient deceased less than one month after transplantation. Values for 10 pediatric patients are shown in footnotes.

^aMedian (IQR) 44.6 (25.0 to 58.9)

^bMedian (IQR) 2.5 (1.5 to 8.4). Mean (SD) 5.3 (4.3) and median (IQR) 3.3 (1.7 to 8.7) for 10 patients.

^cMedian (IQR) 6.2 (5.1 to 8.4)

^dMedian (IQR) 5.2 (4.4 to 6.9). Mean (SD) 5.2 (1.7) and median (IQR) 5.1 (4.2 to 5.7) for 10 patients.

^eMedian (IQR) 11.1 (9.0 to 12.9), $n = 22$

^fMedian (IQR) 8.0 (6.5 to 9.7). Mean (SD) 8.0 (1.9) and median (IQR) 8.0 (6.3 to 9.8) for 10 patients.

^gMedian (IQR) 38.9 (19.3 to 49.4)

^hMedian (IQR) 15.0 (6.1 to 20.1). Mean (SD) 16.2 (15.2) and median (IQR) 11.3 (5.6 to 21.8) for 10 patients.

3.3 | Renal function

3.3.1 | Estimated GFR in pediatric patients

In pediatric patients, eGFRs were on average higher in CLKT than in KT patients (for instance, mean eGFR 82 vs 63 at 1 year) (Figure 2A,B). Both pediatric patient groups exhibited more or less similar change in eGFR during the follow-up. Differences in mean and median eGFR (primary GFR analysis) between groups are shown in Table 3.

TABLE 2 Characteristics of 96 KT control patients

	Adult patients (N = 69)	Pediatric patients (N = 27)
Gender, n (%)		
Male	33 (47.8)	12 (44.4)
Female	36 (52.2)	15 (55.6)
Mean (SD) age at KT, years	44.8 (15.8) ^a	4.9 (4.3) ^b
Mean (SD) CIT, hours	21.8 (4.3) ^c	17.3 (5.3) ^d
Mean (SD) donor age, years	42.0 (13.2) ^e	37.8 (14.6) ^f
Primary indication for KT, n (%)		
Diabetic nephropathy	15 (21.7)	-
CNF	-	15 (55.6)
PKD	11 (15.9)	1 (3.7)
CKD, unspecified	10 (14.5)	3 (11.1)
Chronic glomerulonephritis	8 (11.6)	-
IgA nephropathy	7 (10.1)	-
Chronic tubulointer- stitial nephritis	5 (7.2)	-
Miscellaneous	13 (18.8)	8 (29.6)
KT era, n (%)		
1992-1996	5 (7.2)	-
1997-2001	14 (20.3)	6 (22.2)
2002-2006	33 (47.8)	13 (48.1)
2007-2012	17 (24.6)	8 (29.6)

^aMedian (IQR) 45.1 (23.7 to 59.1).^bMedian (IQR) 2.4 (1.6 to 10.0).^cMedian (IQR) 21.2 (18.8 to 24.7).^dMedian (IQR) 18.4 (16.7 to 21.0).^eMedian (IQR) 45.0 (33.0 to 51.0).^fMedian (IQR) 39.0 (25.3 to 50.2).

In secondary GFR analysis, mean (SD) change in eGFR from one to three years was 20 (24) after CLKT and 8 (17) after KT [difference in mean change of 12 (95% CI -6 to 30; $P = 0.19$)]. In sensitivity analysis, difference in median change was 6 (95% CI -14 to 26; $P = 0.55$). In addition, mean (SD) change in eGFR from three to five years was -15 (16) in CLKT patients and -3 (15) in KT patients with difference in mean change of -12 (95% CI -24 to 0; $P = 0.05$) between groups. In sensitivity analysis, difference in median change of eGFR was -5 (95% CI -17 to 8; $P = 0.44$).

3.3.2 | Measured GFR in pediatric patients

Measured GFRs during the follow-up period for pediatric CLKT and pediatric KT patients are shown in Figure 2C,D. Measured GFRs were also on average higher in CLKT patients compared to KT patients. Differences in mean and median mGFRs (primary GFR analysis) are depicted in Table 3.

In secondary GFR analysis, mean (SD) change in mGFR from one to three years after CLKT was 4 (11) and after KT -1 (6) [difference in mean change of 5 (95% CI -3 to 14; $P = 0.19$)]. In sensitivity analysis, difference in median change of mGFR was 6 (95% CI -4 to 16; $P = 0.26$). In addition, mean (SD) change in mGFR from three to five years in CLKT and KT patients was -8 (15) and -3 (10), respectively. Therefore, the difference in mean change was -5 (95% CI -16 to 6; $P = 0.36$) between groups. In sensitivity analysis, the difference in median change of mGFR was -3 (95% CI -16 to 9; $P = 0.60$).

3.3.3 | Estimated GFR in adult patients

Renal function deteriorated in both adult CLKT and KT patients during the follow-up period albeit the drop in eGFR was more pronounced in CLKT than in KT patients at the beginning (Figure 3). Differences in mean and median eGFRs (primary GFR analysis) are shown in Table 4.

In secondary GFR analysis, mean (SD) change in eGFR from one to three years after transplantation was -11 (13) in CLKT patients and -4 (18) in KT patients with a difference in mean change of -7 (95% CI -14 to 0; $P = 0.05$). In sensitivity analysis, the difference in median change was -9 (95% CI -17 to -1; $P = 0.03$). In addition, mean (SD) change in eGFR from three to five years was -2 (13) in CLKT and -3 (11) in KT patients [difference in mean change of 1 (95% CI -5 to 8; $P = 0.68$)]. In sensitivity analysis, the difference in median change was 0 (95% CI -8 to 8; $P = 0.99$).

Furthermore, results of linear mixed models are shown in Table S3. For instance, there was an approximately 2 to 3 mL/min/1.73 m² decrease in eGFR for every year of follow-up across different models.

3.3.4 | Long-term renal function of pediatric and adult CLKT patients

In five pediatric patients, mean (SD) eGFR and mGFR were 89 (17) and 70 (17) ten years after CLKT, respectively. In pairwise comparison, mean (SD) eGFR increased from 82 (36) to 89 (17) ($n = 5$) from one to ten years after transplantation (95% CI for difference in mean -42 to 28; $P = 0.61$). Furthermore, mGFR remained stable in four pediatric patients with a mean (SD) of 66 (13) at one year and with a mean (SD) of 66 (17) at ten years after transplantation (95% CI for difference in mean -30 to 30; $P = 0.97$).

In nine adult patients, mean (SD) eGFR was 50 (16) ten years after CLKT. In pairwise comparison, mean (SD) eGFR decreased from 66 (24) to 51 (18) ($n = 7$) from one to ten years after transplantation (95% CI for difference in mean 5 to 25; $P = 0.01$).

In sensitivity analyses, bootstrapped CIs were altogether similar in pairwise comparisons (not shown).

3.3.5 | Comparison of estimated GFR and measured GFR in CLKT patients

Mean mGFR was 60 (12) in 10 pediatric patients at last follow-up with a mean (SD) follow-up time of 10.2 (3.9) years after CLKT. Mean

FIGURE 1 Patient survival for 11 pediatric and 23 adult combined liver-kidney transplant (CLKT) patients. One-, five-, and ten-year patient survivals (95% CI) for pediatric patients were 91% (51% to 99%), 91% (51% to 99%), and 81% (42% to 95%), and one-, five-, and ten-year patient survivals (95% CI) for adult patients were 100%, 96% (73% to 99%), and 70% (44% to 85%)

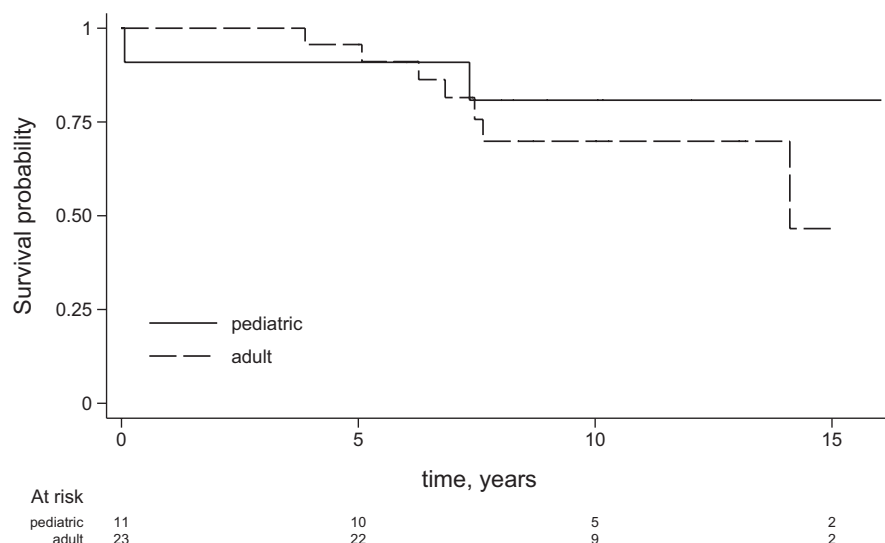
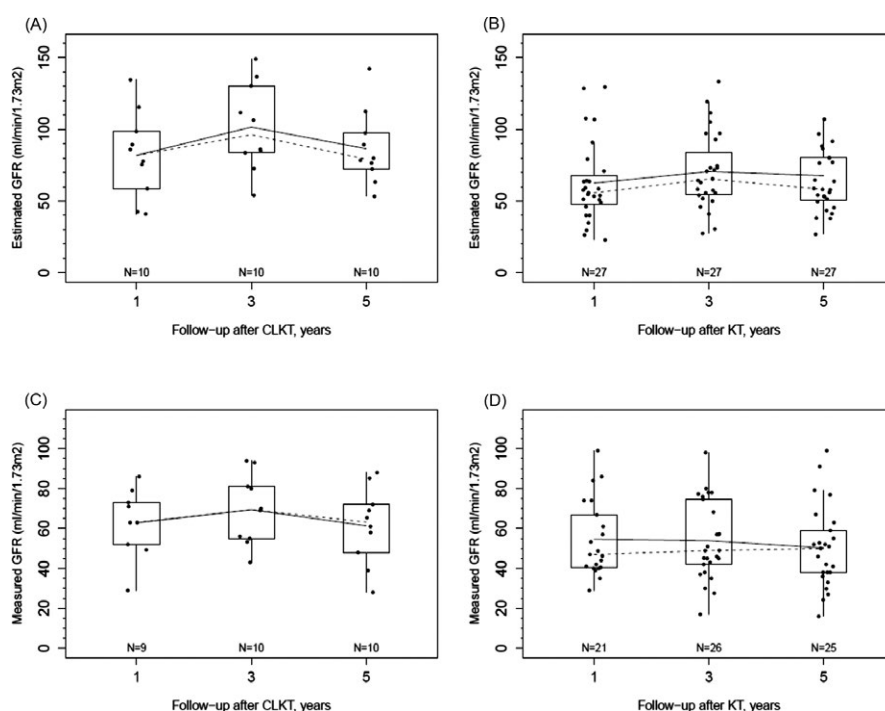


FIGURE 2 Estimated (A and B) and measured (C and D) GFR for pediatric combined liver-kidney transplant (CLKT) patients (A and C) and for pediatric kidney transplant (KT) patients (B and D) after transplantation. Mean and median GFR is shown with black solid and dashed lines, respectively. Mean (median) estimated GFR for CLKT and KT patients at one, three, and five years were 82 (82), 102 (96), 86 (79) and 63 (56), 71 (65), 68 (58), respectively. Mean (median) measured GFR for CLKT and KT patients at one, three, and five years were 63 (63), 69 (70), 61 (63) and 55 (47), 54 (49), 50 (50), respectively. Note the different scale between estimated (A and B) and measured GFR (C and D)



(SD) mGFR was 54 (22) in 12 adult patients taken cross-sectionally during the follow-up with a mean (SD) follow-up time of 6.7 (3.7) years after CLKT.

Mean difference (95% LOA) of estimated minus measured GFR was 14 (−10 to 37) in these 10 pediatric patients and 11 (−12 to 34) in these 12 adult patients (Figure 4). In both pediatric and adult patients, seven eGFRs were within mGFR interval of $\pm 30\%$ reflecting an accuracy (ie, P30) (95% CI) of 70% (40% to 89%) and 58% (32% to 81%) for bedside Schwartz and CKD-EPI equation, respectively.

3.4 | Other results

Correlation coefficients between eGFR and calcineurin inhibitor trough levels are shown in Table S4.

There was no drastic abnormality of selected laboratory tests in pediatric CLKT patients (Table S5). In adult CLKT patients, median total bilirubin was within normal range while mean total bilirubin was elevated due to an outlying value.

4 | DISCUSSION

Our study demonstrates that renal function remained stable in pediatric CLKT patients with long-term follow-up, contrary to what was observed in adult CLKT patients. When renal function of CLKT patients was contrasted to renal function of KT patients, a somewhat similar pattern occurred in eGFR in the transplantation groups during the follow-up period of the pediatric and adult patients.

	Year 1	Year 3	Year 5
Estimated GFR			
Mean (SD)			
CLKT patients ^a	82 (30)	102 (30)	86 (26)
KT patients ^b	63 (28)	71 (26)	68 (32)
Difference (95% CI) ^c	19 (-4 to 42)	31 (8 to 54)	19 (-2 to 40)
Median (IQR)			
CLKT patients	82 (57 to 100)	96 (83 to 131)	79 (71 to 99)
KT patients	56 (47 to 70)	65 (54 to 90)	58 (50 to 80)
Difference (95% CI) ^d	26 (-6 to 58)	31 (2 to 60)	21 (-3 to 45)
Measured GFR			
Mean (SD)			
CLKT patients ^e	63 (17)	69 (17)	61 (19)
KT patients ^f	55 (19)	54 (20)	50 (20)
Difference (95% CI) ^c	8 (-7 to 23)	16 (1 to 30)	11 (-4 to 26)
Median (IQR)			
CLKT patients	63 (51 to 75)	70 (55 to 82)	63 (47 to 73)
KT patients	47 (40 to 69)	49 (42 to 75)	50 (37 to 60)
Difference (95% CI) ^d	16 (-2 to 34)	21 (0 to 41)	13 (-8 to 35)

TABLE 3 Comparison of GFR for pediatric combined liver-kidney transplant and kidney transplant patients

GFRs were estimated with bedside Schwartz equation and measured with ⁵¹Cr-EDTA clearance. GFRs and respective differences are rounded to the nearest whole number and shown with unit of mL/min/1.73 m². IQRs are 25th to 75th percentiles and might slightly differ from Figure 2.

^an=10 at all time-points.

^bn=27 at all time-points.

^cBased on Welch's t test; *P*-values 0.09, 0.01, 0.08 for estimated and 0.27, 0.03, 0.14 for measured GFR at one, three, and five years, respectively.

^dBased on Bonett-Price method; *P*-values 0.11, 0.04, 0.09 for estimated and 0.09, 0.05, 0.23 for measured GFR at 1, 3, and 5 y, respectively.

^en=9, n = 10, n = 10 at 1, 3, and 5 y, respectively.

^fn=21, n = 26, n = 25 at 1, 3, and 5 y, respectively.

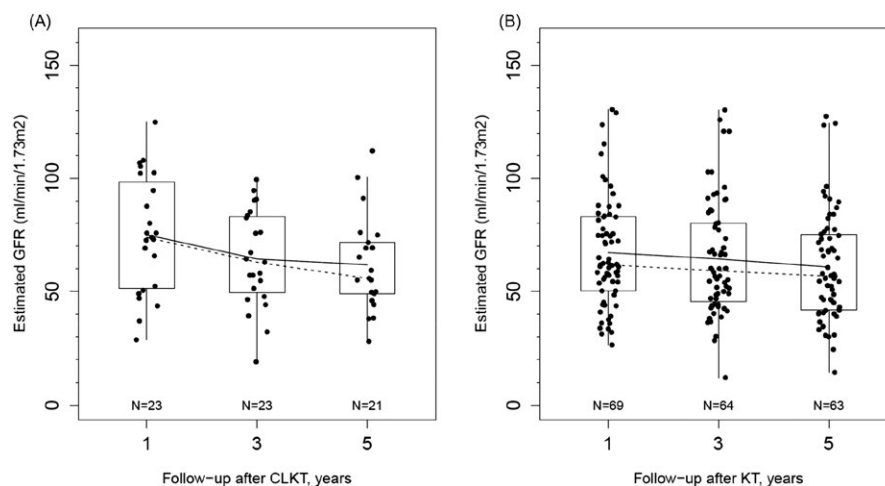


FIGURE 3 Estimated GFR for adult combined liver-kidney transplant (CLKT) patients (A) and for adult kidney transplant (KT) patients (B) after transplantation. Mean and median GFR is shown with black solid and dashed lines, respectively. Mean (median) GFR for CLKT and KT patients at one, three, and five years were 75 (74), 64 (63), 62 (56) and 67 (62), 64 (59), 61 (57), respectively

Our long-term results of eGFR are better or comparable to other pediatric CLKT single-center studies.^{15,27-29} In two of these studies, eGFR was around 70 mL/min/1.73 m² at last evaluation with varying

follow-up times.^{27,28} However, the follow-up times were, on average, shorter than in our cohort. In two other studies, there was a 13 to 18 mL/min/1.73 m² drop in eGFR from one to ten years after

TABLE 4 Comparison of estimated GFR for adult combined liver-kidney transplant and kidney transplant patients

	Year 1	Year 3	Year 5
Estimated GFR			
Mean (SD)			
CLKT patients ^a	75 (26)	64 (21)	62 (21)
KT patients ^b	67 (24)	64 (25)	61 (24)
Difference (95% CI) ^c	8 (-5 to 20)	0 (-11 to 11)	1 (-10 to 12)
Median (IQR)			
CLKT patients	74 (51 to 101)	63 (48 to 83)	56 (48 to 73)
KT patients	62 (50 to 83)	59 (45 to 80)	57 (42 to 75)
Difference (95% CI) ^d	12 (-9 to 33)	4 (-12 to 20)	-1 (-15 to 13)

GFRs were estimated with CKD-EPI equation and are shown with mL/min/1.73 m². GFRs and respective differences are rounded to the nearest whole number. IQRs are 25th to 75th percentiles and might slightly differ from Figure 3.

^an=23, n = 23, and n = 21 at 1, 3, and 5 y, respectively. Mean (median) GFR 77 (78), 66 (66), and 63 (58) when GFRs outside \pm three months were excluded.

^bn=69, n = 64, and n = 63 at 1, 3, and 5 y, respectively. Mean (median) GFR 70 (62), 67 (66), and 61 (56) when GFRs outside \pm three months were excluded.

^cBased on Welch's t test; P-values 0.21, >0.99, and 0.86 at 1, 3, and 5 y, respectively.

^dBased on Bonett-Price method; P-values 0.25, 0.64, and 0.89 at 1, 3, and 5 y, respectively.

CLKT.^{15,29} In contrast, we observed some improvement in eGFR from one to ten years. Additionally, depending on analytical approach, mGFR increased or remained stable in our study between one and ten years. Naturally, there might be number of reasons for these different eGFR patterns observed between our study and these two studies. Unfortunately, mGFRs were not available in either of the two studies.

We observed a decline in renal function of adult CLKT patients during the follow-up period. Although some studies have demonstrated stable renal function after CLKT,¹⁶ similar findings to ours have also been reported by others.^{13,14} Singal et al¹³ demonstrated that eGFR declined in some but not in other patient groups indicating

that primary diagnosis may have a role in renal function after CLKT. Interestingly, mean eGFR in our two primary hyperoxaluria patients with their native kidneys was 51 at one, 96 at five, and 87 at 10 years after CLKT. Ranawaka et al¹⁵ reported mean eGFR around 50 in their primary hyperoxaluria patients from one to ten years after CLKT.

A similar pattern in both adult and pediatric patients occurred when renal function of CLKT patients was assimilated to KT patients. The pediatric CLKT and KT patients showed improvement in eGFR from one to three years after transplantation followed by a downturn from three to five years after transplantation. This pattern was also evident in pediatric CLKT patients but not in pediatric KT

FIGURE 4 Bland-Altman plots for estimated and measured (GFR; mL/min/1.73 m²) in pediatric (A, n = 10) and adult (B, n = 12) combined liver-kidney transplant (CLKT) patients. Bedside Schwartz equation was used in pediatric and CKD-EPI equation in adult patients for GFR estimation. Measured GFRs were taken at last follow-up for pediatric patients and in a cross-sectional manner during the follow-up for adult patients. Mean (SD) difference (black solid line) of estimated minus measured GFR 14 (12) in pediatric and 11 (12) in adult patients. Line above zero indicates overestimation and below zero underestimation of measured GFR with the use of GFR estimation equation. Ninety-five percent LOA are shown with dashed lines

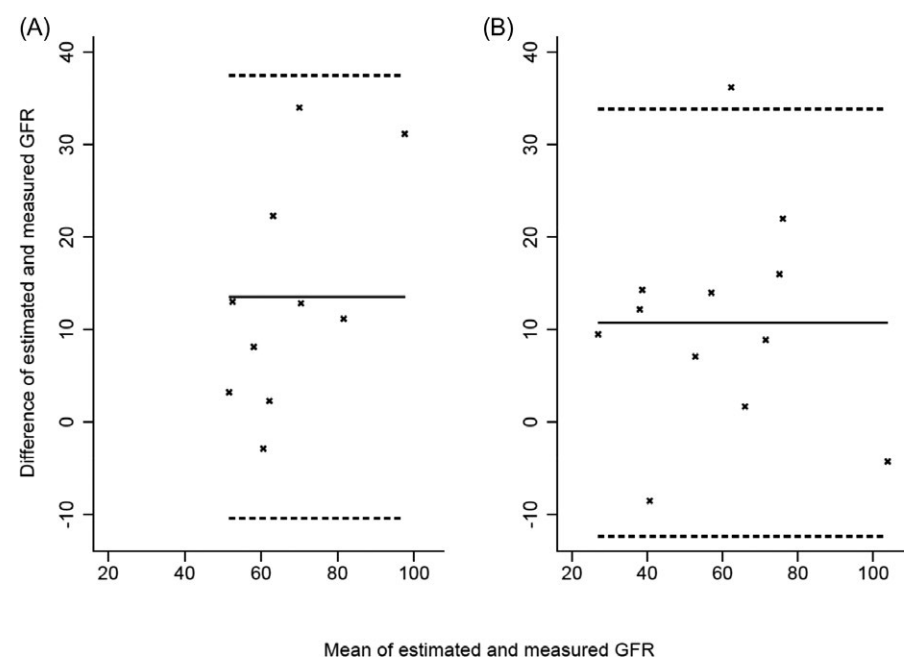


TABLE 5 Characteristics of three studies that have compared renal function of CLKT patients to KT patients

	Study		
	Current study	Ranawaka et al	Taner et al
Patient population	Adult and pediatric	Pediatric	Adult and pediatric
Number of patients			
CLKT	33	40	68
KT	96	40	136
Matching ratio	1:2.9	1:1	1:2
Matched for age and gender	Yes	Age yes (gender no)	Yes
Mean time from CLKT, years	8.8 to 10.2 ^a	6.4	6.2 to 7.1 ^b
Median donor age, y			
CLKT	11 to 39	-	37 to 41
KT	39 to 45	-	39 to 40
Method to determine GFR	Estimation and measurement	Estimation (Schwartz)	Estimation (MDRD)
Time-points for GFR	1, 3, and 5 years	1, 5, and 10 years	4 months and 5 years
Mean GFR at one and five years ^c			
Pediatric CLKT	82 to 86	68 to 59	
Pediatric KT	63 to 68	63 to 52	
Adult CLKT	75 to 62	-	60 to 60 ^d
Adult KT	67 to 61	-	52 to 48 ^e

Mean or median is shown for continuous variables to simplify comparison between current study and two other studies (references 15 and 16).

^aFollow-up time for 23 adult and 10 pediatric CLKT patients, respectively.

^bFollow-up time for 14 DSA-positive and 54 DSA-negative CLKT patients, respectively.

^cEstimated GFRs (mL/min/1.73 m²) at one and five years to simplify comparison between studies. First GFR at four months in Taner et al.

^dValues are rounded and are for DSA-negative CLKT patients. For DSA-positive CLKT patients, respective GFRs 56 to 57.

^eValues are rounded and are for DSA-negative KT patients. For DSA-positive KT patients, respective GFRs 60 to 44.

patients when focused on mGFR. Contrary, adult CLKT and KT patients showed decline in eGFR during the follow-up.

Comparison of our study and two other studies^{15,16} that have contrasted renal function of CLKT patients to KT patients beyond one year after transplantation is shown in Table 5. Ranawaka et al¹⁵ showed that mean eGFR was higher in pediatric CLKT compared to pediatric KT patients which is in line with ours although GFR remained stable in our pediatric patients. Taner et al¹⁶ demonstrated that eGFR deteriorated in KT patients and the deterioration depended on donor-specific antibody status.¹⁶ Our adult CLKT and KT patients had higher mean eGFRs than in study by Taner et al¹⁶ although their patient population consisted of mostly adult but some pediatric patients as well.

Donor age in our pediatric CLKT patients was lower compared to pediatric KT patients, which might explain the on average higher GFRs in pediatric CLKT patients. In the aforementioned study,¹⁶ donor age was not materially associated with graft loss or GFR decline over 50% (ie, functional decline). In a small sample of pediatric KT patients, inclusion of donor age did not improve model performance for GFR prediction.³⁰

GFRs based on estimation equations were on average higher than GFRs based on measurement with ⁵¹Cr-EDTA plasma clearance in our small sample of CLKT patients. In adults, CKD-EPI equation has shown to overestimate or underestimate mGFR in studies with mean follow-up ranging from 5 to 7 years after KT or LT.^{31,32} Mean mGFR was 54 in our adult CLKT patients which is comparable to other studies.^{31,32} There are various GFR estimation equations, and we decided to use CKD-EPI equation. However, both CKD-EPI and MDRD equations have been pointed out as useful in solid organ transplantation population.³³ In pediatric KT patients, bedside Schwartz equation has shown to overestimate mGFR based on a renal inulin clearance albeit providing acceptable 30% accuracy even in lower mGFR levels.³⁴ However, since mGFRs were taken routinely in our pediatric patients, the choice to use one estimation equation over another is less important one.

Our study has some limitations. First, the number of CLKT patients was small. Second, control patients were not selected randomly, which might have introduced selection bias. Future studies should address our study's aforementioned limitations. Our study's

strength is that measured GFRs were routinely taken in our pediatric patients and once during the follow-up from adult CLKT patients, which broadens our long-term renal function results. In addition, all patients were treated and followed at one center by two closely co-operating pediatric and adult units.

From a statistical perspective, our primary and secondary GFR analyses were simple. We assumed that CLKT and KT groups are independent. However, additional analyses for adult patients with linear mixed models were also made to account non-independency of observations. We only adjusted matched variables in addition to group and time according to our modeling objective. Undoubtedly, there can be various factors, such as donor characteristics or immunological aspects (for example, donor-specific antibodies) among other things that might have effect on observed renal function. We opted out of linear mixed models in pediatric patients since the number of patients was small. We did not dichotomize our results to statistically significant or non-significant since there are problems with this approach, as has been emphasized elsewhere³⁵ and also in transplantation literature.³⁶

In conclusion, longitudinal changes in GFRs were somewhat similar in CLKT and KT patients in both age-groups but pediatric CLKT patients had on average higher GFRs than pediatric KT patients. Renal function remains stable with long-term follow-up in pediatric CLKT patients but declines in adult CLKT patients.

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CONFLICT OF INTEREST

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AUTHORS' CONTRIBUTIONS

JMK: performed the statistical analyses, participated in the data collection, and wrote the article. ML: participated in research design and performed the research. CH: participated in research design and wrote the article. HJ: participated in the performance of

the research. MPP: participated in research design. HI participated in research design, performed the research, and wrote the article. JL: participated in research design and wrote the article. All authors accepted the final version of the manuscript.

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SUPPORTING INFORMATION

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